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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Ken Sonnenfeld, Esq.
MORGAN & FINNEGAN LLP
345 Park Avenue
New York, NY 10154

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,432	WAUGH ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *2-9,13,14,18,22 and 28-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10-12,15-17,19-21,23-27 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In the restriction requirement mailed 5/19/04, three groups were set forth and a subsequent restriction between positively charged branching groups was made, wherein claims 1 and 19 were considered to link the various positively charged branching groups.

In the response filed 6/21/04 Applicant elected group 1, claims 2-18 and 20-27 and the following species of the invention: a composition comprising a non-covalent association complex of a positively charged backbone, "a second negatively-charged backbone having a plurality of attached targeting moieties", and "a third negatively-charged backbone having a plurality of attached biological agents. As a biological agent, Applicant elected the species of botulinum toxin. At that time Applicant did not elect a positively charged branching group.

On 9/17/04 a notice of non-responsive amendment was sent, and the restriction requirement was clarified. In the response filed 6/13/05, Applicant elected SEQ ID NO:19 as the positively charged branching group. By Applicant's response, it was apparent that the requirement for restriction between positively charged branching groups was interpreted as a species election requirement. This was not the intent of the Examiner, the requirement was set forth as a restriction between groups of inventions, not species. However, in the interest of simplicity, the positively charged branching groups will be considered to be species, rather than linked inventions. As a result, the groups are considered to be: Group 1, claims 1-27, Group 2, claims 28-37, and Group 3, claims 38 and 39.

In the response filed 6/21/04 election was made with traverse. Traversal was on the grounds that the claimed inventions could be searched without undue burden. This is not found persuasive because the claimed compositions could be used for delivery to cells in vitro and need not comprise a pharmaceutical carrier. Applicant's arguments were persuasive regarding claim 39, and it is rejoined.

The requirement is still deemed proper and is therefore made FINAL.

A search indicates that the elected invention, a composition comprising a non-covalent association complex of a positively charged backbone with attached positively charged branching groups that are SEQ ID NO: 19, a second negatively-charged backbone having a plurality of attached targeting moieties, and a third negatively-charged backbone having a plurality of attached biological agents, is free of the art. Because the elected invention is free of the prior art, the PTO has selected another invention for consideration, i.e. a composition comprising a non-covalent association complex of a positively charged backbone that is a peptide comprising positively charged branching groups that are fragments of HIV-TAT, at least one member selected from the group consisting of RNA, DNA, ribozymes, modified oligonucleotides and cDNA encoding a selected transgene, and DNA encoding at least one persistence factor, wherein the fragments of HIV-TAT are other than:

1. $G_{n1}R_{n2}$ with n1 = an integer from about 0 to about 20, and n2 = an odd integer from about 5-25,

2. G_p-RGRDDRRQRRR-G_q, (SEQ ID NO:19), and

3. G_p-YGRKKRRQRRR- G_q, (SEQ ID NO:20), as set forth in the restriction requirement of 5/19/04.

Claims 1, 10-12, 19-21, 23-27 and 39 read on the species under consideration. Claims 15-17 are free of the prior art to the extent that they read on SEQ ID NO:19, and are under consideration to that extent.

Claims 2-9, 13, 14, 18, 22, and 28-38 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 28-38 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/21/04.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10-12, 15-17, 19, 20, 23-27 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependents, and claim 39, require at least 2 members selected from the group consisting of:

i) a first negatively-charged backbone having a plurality of attached imaging moieties;

ii) a second negatively-charged backbone having a plurality of attached targeting agents;

iii) at least one member selected from the group consisting of RNA, DNA, ribozymes, modified oligonucleotides and cDNA encoding a selected transgene;

iv) DNA encoding at least one persistence factor; and

v) a third negatively-charged backbone having a plurality of attached biological agents.

The claims are indefinite because items ii) and iv) require a second and third negatively charged backbone, respectively, but the claim has no clear requirement for a first negatively charged backbone. As a result it is unclear as to whether a first negatively charged backbone should be understood as part of the invention when groups ii and iii are elected, or whether groups ii and iii would simply be regarded as a first and second negatively charged backbone, respectively, in the absence of a first negatively charged backbone.

Claim 10 is indefinite because it is unclear what is intended by the term "length". The specification does not define this term and it is not clear what standard should be used to determine length. One standard that could be used is the length of the backbone in angstroms, another is the length of the backbone in terms of the number of monomers comprised, still another is the length of the backbone after it has folded as a result of interactions with the other members of the complex. It is also unclear if, in the situation where a complex comprises more than one of a given negatively charged backbone, all of the copies of that backbone should be used in the calculation.

Because one of skill does not know which standard to apply, or what are the limits of how the length calculations can be performed, one cannot know the intended metes and bounds of the claims.

Claims 15-17 are indefinite because SEQ ID NO:19 is not an "HIV-TAT fragment" as required by claim 12. A sequence search by the PTO did not find that the sequence of SEQ ID NO:19 occurred in HIV TAT. In particular, the two aspartate residues at positions 4 and 5 of SEQ ID NO:19 do not occur in HIV TAT. Instead these two residues are generally lysine residues in the known sequences of TAT. Furthermore, the C- and N-terminal glycine multimers are not present in HIV-TAT.

Claims 19, 20, and 23-27 are indefinite because it is unclear what are the metes and bounds of "attached efficiency group". The claims require a "non-covalent association complex of a positively charged backbone having at least one attached efficiency group and at least one nucleic acid member". It is unclear as to whether the "efficiency group" must be attached to the backbone in a covalent manner, or whether this limitation applies only to the nucleic acid member. Claim 1 is drawn to a "non-covalent association complex" that comprises a negatively-charged backbone with attached imaging, targeting, or biological agents. However, in light of the specification at page 10, lines 26-28 these agents can be covalently attached to the negatively-charged backbone. Because the specification appears to use the term "attached" to indicate both covalent and non-covalent bonds, it is unclear what is the nature of the attachment between the "efficiency group" and the positively charged backbone in claim 19.

Response to Arguments

The issue of the indefiniteness of claim 1 and dependents for requiring a "second" and/or "third" negatively charged backbone without requiring a first negatively charged backbone was first raised in the restriction requirement. Applicant responded in the submission filed 6/21/04. Applicant's arguments were fully considered, but are unpersuasive.

Applicant asserted that the words "first", second", and "third" simply enumerate different possible elements from which a practitioner can choose when practicing the invention. Applicant asserts that it does not imply the number of elements or any order of elements. This is unpersuasive because "first", second", and "third" clearly refer to numbers, and can clearly be interpreted as requiring precedence of negatively charged backbones. The claims can clearly be interpreted as requiring group i) to be present whenever group ii) is present, and of requiring groups i) and ii) to be present whenever group v) is present.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following rejection of claim 19-21 is applied to a generic form of the claims that is not limited to the species under consideration. This rejection demonstrates the unpatentability of the generic claims not limited to a species.

Claims 19-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Illum (US Patent 5,744,166).

Illum taught non-covalent complexes of polycations and nucleic acids. One exemplary polycation is polylysine modified with polyethylene glycol (PEG). See abstract; column 3, lines 16-19 and 57; and column 4, lines 4-7. PEG is considered to be an "efficiency group", as per claim 19.

Thus Illum anticipates the claims.

The following rejections address the species under consideration.

Claims 1, 11, 12, 19-21, 23, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al (J. Biol. Chem 262(10): 4429-4432, 1987) as evidenced by GenBank Accession No. M77788 (2005).

Wu taught non-covalent complexes of plasmid pSV2 CAT and polylysine, wherein the polylysine comprised an attached asialoorosomucoid targeting ligand. See abstract. The targeting ligand is considered to be an "efficiency group", as per claim 19. Plasmid pSV2 CAT comprises a selectable marker (beta lactamase, i.e. ampicillin resistance) as evidenced by GenBank Accession No. M77788. The selectable marker is considered to be a persistence factor as required by claim 1. Regarding claims 11, 12 and 21, polylysine is a polymer comprising attached positively charged branching

groups, i.e. domains, which are also present in HIV-TAT because lysine is present in HIV TAT.

Thus Wu anticipates the claims.

Claims 1, 11, 12, 19-21, 23, 24, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Cristiano et al (Proc. Nat. Acad. Sci. USA 90: 11548-11552).

Cristiano taught non-covalent complexes of polylysine and plasmid pCMV betaGal. The polylysine comprised attached targeting ligands, e.g. adenovirus and asialoorosomucoid. See abstract. The plasmid comprised a beta galactosidase reporter gene under control of a CMV promoter. See page 11548, column 2, second full paragraph. Plasmid pCMV beta gal comprises a selectable marker considered to be a persistence factor as required by claim 1. Regarding claims 11, 12 and 21, polylysine is a polymer comprising attached positively charged branching groups, i.e. domains, which are also present in HIV-TAT because lysine is present in HIV TAT.

Thus Cristiano anticipates the claims.

Claims 1, 11, 12, 19-21, 23-25, and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Puls et al (Gene Therapy 6: 1774-1778, 1999), as evidenced by http://www.genlantis.com/catalog/product_line.cfm?product_family_key=13&product_line_key=54, retrieved from the internet on 9/2/05.

Puls taught non-covalent complexes of polylysine and plasmid pGeneGrip encoding green fluorescent protein (GFP) under the control of a CMV promoter and a

selectable marker (see map on second page of attached product information downloaded from the web site cited above). The polylysine comprised an attached antibody targeting ligand. See abstract. Regarding claims 11, 12 and 21, polylysine is a polymer comprising attached positively charged branching groups, i.e. domains, which are also present in HIV-TAT because lysine is present in HIV TAT.

Thus Puls anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 10-12, 19-21, 23, 24, 27 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (US Patent 5,744,166) in view of the 1998 Promega Catalog.

Illum taught non-covalent complexes of polycations and nucleic acids encoding genes. One exemplary polycation is DEAE-dextran of molecular weight 5000 to 40 $X10^6$ Da, another is polylysine. See abstract; column 3, lines 16-32, and 57.

Illum did not require that the DNA must encode a persistence factor, or specify any relationship between the length of the polycation and the length of the nucleic acid.

One of ordinary skill in the art appreciates that in order to obtain expression of a gene, the gene must be operably linked to expression control sequences such as a

promoter. This is conveniently achieved by inserting a gene of interest into a plasmid expression vector, such as the mammalian expression vectors disclosed at pages 262-265 of the 1998 Promega catalog. These plasmids have the added advantage of selectable markers that allow amplification of the plasmid in bacterial cells or selection of transfectants in mammalian cells. For the purpose of this rejection, selectable markers are considered to be persistence factors, as recited in claim 1. Furthermore, the SV40 poly A sites in each of the disclosed vectors are considered to be persistence factors inasmuch as they play a role in stabilizing expressed mRNAs, and the plasmid replication origins are also considered to encode persistence factors inasmuch as they allow replication of the plasmids. Note also that three of the four vectors include CMV promoter/enhancers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to insert a gene of Illum into any one of the expression vectors disclosed by Promega, prior to incorporation into the composition of Illum. One would have been motivated to do so because such plasmids facilitate handling of nucleic acids by allowing amplification in bacterial hosts prior to delivery to mammalian hosts.

Illum taught a range of DEAE-dextran of molecular weights from 5000 to 40 $X10^6$ Da. Assuming a monomer molecular weight of about 217 Da per monomer, this corresponds to DEAE-dextran lengths of about 23 to about 184000 monomers. The "preferred " molecular weight of 500,000 Da corresponds to about 2300 monomers. The monomer lengths of the Promega plasmids carrying an average gene of 2 kb would range from about 5.6 to about 7.8 kb. It would have been obvious to one of ordinary

skill in the art, as a matter of routine optimization to select the length of DEAE dextran that gave the optimal transfection efficiency for a given plasmid DNA. Absent evidence of unexpected results it would have been obvious to arrive at a length of DEAE-dextran, in monomers, in the range of about 1 to about 4 times the length the plasmid DNA in base pairs.

With regard to claim 11, note that DEAE-dextran is a polymer comprising attached positively charged branching groups.

With regard to claims 11 and 12, Note that Illum also exemplified polylysine as a polycation for use in the invention. Polylysine is a polymer comprising attached positively charged branching groups which are also present in HIV-TAT because lysine is present in HIV TAT. Use of polylysine in the formation of complexes with plasmid DNAs comprising selectable markers would render claims 1, 11 and 12 obvious.

Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize the elements of the invention of Illum into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was prima facie obvious.

Claims 19, 24, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Puls et al (Gene Therapy 6: 1774-1778, 1999) in view of Luo et al (US Patent 6,280,937) and

http://www.genlantis.com/catalog/product_line.cfm?product_family_key=13&product_line_key=54,

retrieved from the internet on 9/2/05.

Puls taught non-covalent complexes of polylysine and plasmid pGeneGrip encoding green fluorescent protein (GFP) under the control of a CMV promoter and a selectable marker (see map on second page of attached product information downloaded from the web site cited above). The polylysine comprised an attached antibody targeting ligand which is considered to be an efficiency group. See abstract. Regarding claims 11, 12 and 21, polylysine is a polymer comprising attached positively charged branching groups, i.e. domains, which are also present in HIV-TAT because lysine is present in HIV TAT.

Puls did not teach a nucleic acid encoding blue fluorescent protein.

Luo taught that blue fluorescent protein and green fluorescent proteins could be used as alternative markers for detection. See column 6, lines 45-57. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (J. Biol. Chem 262(10): 4429-4432, 1987) in view of GenBank Accession No. M77788 (2005).

Wu taught non-covalent complexes of plasmid pSV2 CAT and polylysine, wherein the polylysine comprised an attached asialoorosomucoid targeting ligand. See abstract. Plasmid pSV2 CAT comprises a selectable marker (beta lactamase, i.e. ampicillin resistance) as evidenced by GenBank Accession No. M77788. The selectable marker is considered to be a persistence factor as required by claim 39.

Wu did not teach organization of the polycation and nucleic acid into a kit.

It would have been obvious to one of ordinary skill in the art at the time of the invention to organize the elements of the invention of Wu into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.